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DOREEN M HOGLE ESQ
HAMILTON BROOK SMITH & REYNOLDS PC
TWO MILITIA DRIVE
LEXINGTON MA 02421-4799

EXAMINER	
JOHANNSEN,D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/407,660	Applicant(s) Lander et al
	Examiner Diana Johannsen	Group Art Unit 1655

☒ Responsive to communication(s) filed on *Apr 21, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-27 and 42-49 are indefinite over the recitation of the terms "identifying" and "identify" in claims 1, 14, 42, 44, and 46-48. It is unclear as to what is intended to be encompassed by this terminology. Particularly, it is unclear as to whether this language refers to a type of active method step (e.g., to a step of detecting one or more polymorphisms, fragments, etc.), or whether this language may encompass purely mental steps or processes of "identification". The claims should be amended so as to set forth the actual, active method steps necessary to carry out the claimed methods.

Claims 1-45 and 48-49 are indefinite over the recitation of the terms "analyzing" and "analyzed" in claims 1, 14, 28, 42, 44, and 48. These terms are vague and indefinite, as such language does not apprise one of skill in the art as to what actual steps must be taken to perform the claimed methods. Further, it is unclear as to whether such language requires an actual active

step, or whether the terms "analyzing" and "analyzed" may encompass solely mental steps of "analysis". Accordingly, the claims should be amended so as to set forth active process steps.

Claims are indefinite over the recitation of the terms "selected" and "selecting" in claims 1, 12, 14, 24, 28, 31, and 46-48. It is unclear as to what is intended to be encompassed by this terminology. Particularly, it is unclear as to whether this language refers to a type of active methods step (e.g., to a step of isolating fragments), or whether this language may encompass purely mental steps or processes of "selection" (e.g., mentally "selecting" a particular fragment that has been visualized on a gel). The claims should be amended so as to set forth the actual, active method steps necessary to carry out the claimed methods.

Claims 1-27 and 44-49 are indefinite over the recitation of the phrases "corresponding to the same chromosomal location" in claim 1, 14, and 48, and "corresponding chromosomal locus" in claims 46-47. It is unclear as to what type or types of relationships between a nucleic acid and a chromosomal location or locus are intended to be encompassed by the term "corresponding". Accordingly, it is unclear as to what actual steps must be carried out in order to practice the claimed methods, and the metes and bounds of the claims are unclear. Clarification is required.

Claims 1-13 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. The claims are drawn to methods "for identifying a collection of polymorphisms from nucleic acid molecules in a sample", yet recite a final step of "comparing pairs of orthologous sequences to identify polymorphisms between said sequences". The claims do not set forth how comparing pairs of orthologous sequences results in "identifying a collection

of polymorphisms". Accordingly, it is unclear as to whether the claims are intended to be limited to methods for identifying a collection of polymorphisms or to methods for comparing orthologous sequences to "identify polymorphisms between said sequences".

Claims 6-7 and 19-20 are indefinite over the recitation of the term "particular" in claims 6 and 19. It is unclear as to how the term "particular" is intended to further limit the term "trait". Specifically, it is unclear as to how a "particular trait" would differ from a "trait". Clarification is required.

Claims 8-9 are indefinite over the recitation of the phrase "wherein step (b)(i) is performed by one or more restriction endonucleases". This language suggests that restriction endonucleases will carry out a method step, rather than indicating the manner in which restriction endonucleases are to be employed in the claimed method. Clarification is required.

Claim 26 is indefinite over the recitation of the language "wherein the one or more restriction endonucleases cleave DNA on average about once every 2000 base pairs". The instant claim is not limited to, e.g., DNA obtained from a particular source, and it is well known to those of skill in the art that the frequency with which a particular restriction enzyme will "cleave DNA" is dependent upon the origin of that DNA, among other factors (see paragraph 12, below). Accordingly, it is unclear as to how this language is intended to further limit the method of claim 14. Clarification is required.

Claims 28-43 and 48-49 are indefinite for failing to recite final process steps that clearly relate back to the claim preambles, and over the recitation of the language "method for

genotyping" and "analyzing...to assess the genotype" in claims 28 and 48. First, while the instant claims are drawn to methods "for genotyping a nucleic acid sample for polymorphisms" (claims 28-43) and "for genotyping a nucleic acid-containing sample...for polymorphisms" (claims 48-49), the claims recite final process steps, respectively, of "analyzing...to assess the genotype at one or more polymorphic sites" and "analyzing...to assess the genotype at one or more polymorphisms". The claims do not clearly indicate what one must do in order to actually accomplish "genotyping", and particularly, it is unclear as to whether, e.g., detection of one polymorphism would be considered to constitute "genotyping...for polymorphisms". Second, it is unclear as to whether Applicant's intent is to claim a method of "genotyping" in which polymorphisms are detected and compared to known genotypes, or whether Applicant's intent is to claim a method of, e.g., detecting previously unknown polymorphisms or groups of polymorphisms which are considered to constitute a "genotype". Accordingly, the metes and bounds of the instant claims are unclear.

Claims 33-35 are indefinite over the recitation of the term "specific oligonucleotide linker sequences". It is unclear as to how the term "specific" is intended to modify the "oligonucleotide linker sequences". Particularly, it is unclear as to how a "specific" linker sequence might differ from a linker sequence. Clarification is required.

Claims 37, 39, and 41 are indefinite because it is unclear as to how the claims are intended to further limit claim 33, from which they depend. Claim 33 indicates that "step (c) is performed by attaching specific oligonucleotide linker sequences to the fragments in the reduced representation and then amplifying said fragments". However, each of claims 37, 39, and 41

recite a different method that is to be "performed" for step (c). It is not clear as to whether the steps recited in claims 37, 39 and 41 are to be performed in lieu of the process set forth in claim 33 (in which case claims 37, 39, and 41 are not proper dependent claims), or whether (and how) the steps of claims 37, 39 and 41 might be intended to modify the limitations set forth in claim 33. Clarification is required.

Claims 42-45 are indefinite over the recitation of the limitation "the sequences of the two members of a proposed pair" and "proposed pairs" in claims 42 and 44. First, there is insufficient antecedent basis for the language "the sequences of the two members of a proposed pair", as claims 1 and 14, from which the instant claims depend, do not recite or refer to "two members of a proposed pair", or to "sequences" thereof. Second, it is unclear as to what types of pairs might be considered to be "proposed" pairs, and as to how such pairs relate back to the "pairs of fragments" of claims 1 and 14. Clarification is required.

Claims 42-45 are indefinite over the recitation of the phrase "identical over 10 or more bases within the first 50 bases and the last 50 bases of the sequences". It is unclear as to whether this language is intended to require identity over 10 bases combined, or over 10 bases within each of the first and last 50 bases of "the sequences". Further, it is unclear as to whether the language "identical over" is intended to require identity over 10 contiguous bases, or whether the claims are intended to encompass identity at any 10 positions within the first and/or last 50. Clarification is required.

Claims 42-45 are indefinite over the recitation of the term "candidate single nucleotide polymorphisms" in claims 42 and 44. It is unclear as to what is meant by this language, and particularly, as to how a "candidate single nucleotide polymorphism" would differ from a "single nucleotide polymorphism" within the context of the claimed invention. Clarification is required.

Claims 42-45 are indefinite over the recitation of the phrase "determining the number of candidate matches for the same chromosomal location, wherein said candidate matches are accepted if said number of matches does not exceed expectations". First, the is insufficient antecedent basis for the term "the same chromosomal location", and it is unclear as to what the scope of this term might be. Second, it is unclear as to whether the language "matches are accepted" requires an actual, active method step, and if so, as to what actual steps would be required to accomplish "acceptance". Third, the phrase "if said number of matches does not exceed expectations" renders the claims vague and indefinite. It is unclear as to what might constitute "expectations", and as to how a number that "does not exceed expectations" would be established or determined. Clarification is required.

Claims 43 and 45 are indefinite over the recitation of the phrase "wherein said expectations are determined according to binomial or Poisson distributions". This language does not apprise one of skill in the art as to what actual active steps are to be taken in order to determine expectations. Accordingly, it is unclear as to <u>how</u> one is to employ "binomial or Poisson distributions" to determine expectations. The claims should be amended so as to recite active method steps.

Claims 46-47 are indefinite over the recitation of the language "determining a limited population of polymorphism". It is unclear as to whether this language is intended to require one to merely detect the presence of a "limited population of polymorphisms", or whether Applicant's intent is to require one to determine what particular polymorphisms are present in a population. Further, it is unclear as to how the term "limited" is intended to further limit the "population of polymorphisms". In other words, how would a "limited population of polymorphisms" differ from a "population of polymorphisms"? Clarification is required.

Claim 49 is indefinite because it is unclear as to how it is intended to further limit claim 48. The claim is drawn to "A method according to Claim 48, wherein the second nucleic acid-containing sample is treated by a method identical to step (b)". It is unclear as to whether this step is to be performed in addition to the steps set forth in claim 48, or whether this recitation is intended to further limit step (f) of claim 48. The claim should be amended so as to clarify the manner in which it is intended to modify the method of claim 48.

Claim Rejections - 35 U.S.C. § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4, 8-10, 12-17, 21-22, 24-29, 31-32, and 46-49 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gu et al (BioTechniques 24(5):836-837 [5/1998]).

It is noted that provisional application no. 60/102,069 does not disclose methods comprising a step in which a reduced representation is analyzed "to identify pairs of fragments corresponding to the same chromosomal location, wherein fragments corresponding to the same chromosomal location are orthologous sequences", as required by instant claims 1, 14, and 48, and claims dependent therefrom, or a step of selecting fragments "which occur at a corresponding chromosomal locus, thereby producing a pair", as required by instant claims 46-47. Further, with respect to claim 28 and claims dependent therefrom, while the provisional application discloses the preparation of genotyping chips and arrays (see, e.g., p. 7, p. 15), the provisional application does not disclose methods for genotyping as set forth in claim 28, wherein fragments in a reduced representation are "analyzed" to "assess the genotype at one or more polymorphic sites". Accordingly, Applicants are entitled to a priority date of September 28, 1999 with respect to the instant claims, and the Gu et al reference is available as prior art under 35 U.S.C. 102(b).

Gu et al teach a method of identifying single nucleotide polymorphisms (SNPs) (see entire reference). In Gu et al's method, nucleic acid samples are amplified, amplification products are digested with multiple restriction enzymes, and fragments are separated by size on a gel, allowing visualization of heteroduplexes which are indicative of polymorphisms (p. 836). Gu et al exemplify the use of their method in the detection of SNPs in the canine *APOH* gene (p. 836-837). With respect to independent claims 1 and 14 and claims dependent therefrom, Gu et al's

methods result in the "identifying" of a collection of polymorphisms. Further, Gu et al teach a method in which samples are obtained and treated to "produce a reduced representation" by restriction digestion and size fractionation; it is an inherent property of the restriction digestion step taught by Gu et al that it is "sequence-dependent". Gu et al's methods further require identification of pairs of fragments that "correspond to the same chromosomal location" (e.g., two different alleles of the *APOH* gene), and comparison of such pairs by visualization of heteroduplexes, as well as by sequencing. With respect to independent claims 28 and 48 and claims dependent therefrom, Gu et al exemplify the use of their method in canine genotyping (p. 836-837). With respect to independent claims 46-47, it is an inherent property of Gu et al's method that it results in the detection/determination of a "limited population of polymorphisms", as required by the claims. With respect to claims 3 and 16, Gu et al teach samples pooled from more than one individual (p. 836). With respect to claims 4 and 17, Gu et al exemplify analysis of DNA samples. With respect to claims 9 and 21, Gu et al exemplify digestion with enzymes including *Hae*III (p. 836). With respect to claims 10, 22, and 29, Gu et al teach the use of agarose gels in separation (p. 836). With respect to claims 12, 24 and 31, Gu et al teach selection of heteroduplexes, which constitute fragments comprising one allele hybridized to another allele (p. 836). With respect to claims 13, 25, and 32, Gu et al teach the sequencing of orthologous sequences (p. 837). With respect to claim 26, it is noted that the instant claim is not limited to "DNA" from a particular source, and it is well known to those of ordinary skill in the art that the frequency with which a particular restriction enzyme will "cleave DNA" is dependent upon the

origin of that DNA, among other factors. Further, it is an inherent property of at least some of the enzymes taught by Gu et al that these enzymes cleave some types of DNA samples "on average about once every 2000 base pairs", as required by the claim (see paragraph 12, below). With respect to claim 27, Gu et al teach "selection" of a subset of fragments ranging in size "from 150 to 400 bp" (p. 836), and exemplify "selection" of fragments ranging from 90-480 bp (Fig. 1). With further respect to claims 48-49, it is noted that Gu et al exemplify subsequent detection of a polymorphism identified by their methods by PCR, followed by *Aci*I digestion and size separation (p. 837). Accordingly, Gu et al clearly anticipate each of the instant claims.

Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 6-7, 19-20, 36, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al (BioTechniques 24(5):836-837 [5/1998]) in view of Landegren et al (Genome Res. 8(8):769-776 [8/1998]).

Gu et al teach a method of identifying single nucleotide polymorphisms (SNPs) (see entire reference). In Gu et al's method, nucleic acid samples are amplified, amplification products are digested with multiple restriction enzymes, and fragments are separated by size on a gel, allowing visualization of heteroduplexes which are indicative of polymorphisms (p. 836). Gu et al exemplify the use of their method in the detection of SNPs in the canine *APOH* gene (p. 836-837). Gu et al's methods result in the "identifying" of a collection of polymorphisms. Further, Gu et al teach a method in which samples are obtained and treated to "produce a reduced representation" by restriction digestion and size fractionation; it is a property of the restriction digestion step taught by Gu et al that it is "sequence-dependent". Gu et al's methods further require identification of pairs of fragments that "correspond to the same chromosomal location" (e.g., two different alleles of the *APOH* gene), and comparison of such pairs by visualization of heteroduplexes, as well as by sequencing. Gu et al exemplify the use of their method in canine genotyping (p. 836-837). Gu et al do not teach or suggest identification of polymorphisms found in individuals that share traits, including individuals sharing a disorder, as required by instant claims 6-7 and 19-20. Further, Gu et al do not teach or suggest employing in their methods steps

of single-base extension, hybridization to an array, and/or oligo ligation, as required by claims 36, 38, and 40.

Landegren et al teach that "SNPs are expected to take the place of simple tandem repeat polymorphisms - microsatellites - as markers in disease gene mapping", that SNPs are more stably inherited than microsatellites, and that identification of SNPs may facilitate detection and understanding of mechanisms underlying disease (p. 769). Accordingly, in view of the teachings of Landegren et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Gu et al's method so as to have identified polymorphisms common to individuals sharing a trait, including individuals suffering from a particular disorder. An ordinary artisan would have been motivated to have modified the method of Gu et al in this manner for the advantage of rapidly identifying novel, candidate disease-linked or disease-causing polymorphisms shared by individuals having a disorder of interest.

Furthermore, in view of the teachings of Landegren et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the "analyzing" step (step (c)) of Gu et al's method so as to have conducted "analysis" to "assess the genotype at one or more polymorphic sites" using steps of single-base extension, hybridization to an array, and/or oligo ligation. Landegren et al teach that each of these procedures are well known methods for rapid detection and differentiation of SNP's (see entire reference). Specifically, Landegren et al disclose that minisequencing of SNPs, which comprises a step of single base extension, may be used for rapid analysis of multiple SNPs in a homogeneous format

(p. 773). Similarly, Landegren et al teach that array hybridization may allow one to "analyze many SNPs in parallel" (p. 771) and, in combination with multiplex amplification, "greatly extend the number of SNPs analyzed at one time" (p. 774). Landegren et al also teach that SNP analysis by oligonucleotide ligation assay permits rapid, real-time detection of SNPs in a homogeneous format (p. 772-773). Accordingly, an ordinary artisan would have been motivated to have modified the method of Gu et al in order to have rapidly identified multiple polymorphisms in a homogeneous format, as taught by Landegren et al, for the advantages of improved efficiency and ease of detection.

8. Claims 5 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Wu et al (DNA 8(2):135-142 [1989]).

The teachings of Gu et al are set forth in paragraph 7, above. Gu et al do not teach or suggest analyzing RNA molecules to "identify" a collection of polymorphisms. Wu et al teach that identification of SNPs in RNA samples allows one to analyze the presence of mutations in mRNA by, e.g., determining the ratio of normal:mutant gene transcripts expressed in an individual (p. 139). Wu et al teach that methods of SNP analysis may be "applied equally to DNA and RNA, making it possible to analyze the expression of polymorphic sequences" (p. 140). In view of the teachings of Wu et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gu et al so as to have analyzed an RNA sample. An ordinary artisan would have been motivated to have made such a

modification for the advantage of detecting and analyzing the presence of polymorphisms in expressed genes, as suggested by Wu et al.

9. Claims 11, 23, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Bonn et al (U.S. Patent No. 5, 585,236 [12/1996]).

The teachings of Gu et al are set forth in paragraph 7, above. Gu et al do not teach or suggest a step of separating "fractionated" nucleic acids that is "performed using high pressure liquid chromatography (HPLC)", as required by the instant claims. Bonn et al teach an HPLC-based method of nucleic acid separation (see entire reference). Bonn et al teach that their method may be used to separate fractionated nucleic acids (col 3, lines 23-27), and that their separation method is more efficient that gel electrophoresis, which they describe as "a rather laborious procedure consisting of many labor intensive steps that are inaccessible to automation" (col 2, lines 36-38; col 5, line 42-col 6, line 13). In view of the teachings of Bonn et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gu et al so as to have separated restricted/fractionated nucleic acids by the chromatographic method of Bonn et al. An ordinary artisan would have been motivated to have made such a modification for the advantage of improving the efficiency of nucleic acid separation and facilitating adaptation of the method for automation, as suggested by Bonn et al.

10. Claims 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Drmanac (U.S. Patent No. 6,025,136 [2/2000; effective filing date 12/1994]).

The teachings of Gu et al are set forth in paragraph 7, above. While Gu et al teach the sequencing of orthologous sequences (p. 837), Gu et al do not teach or suggest particular steps that may be taken to accomplish sequencing. Drmanac discloses that the sequencing of multiple restriction fragments of interest may be accomplished by methods in which fragments are amplified by cloning and/or PCR, and specifically teaches ligation of adaptors to restriction fragments and amplification of those fragments with primers that hybridize to adaptor sequences (Examples 7 and 8). Drmanac teaches that the use of universal primers complementary to adaptor sequences allows one to amplify a large number of target fragments of interest using a single primer pair (col 9, lines 29-33). In view of the teachings of Drmanac, it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of Gu et al so as to have employed Drmanac's methods for sequencing. As Gu et al does not provide specific guidance with respect to how fragments of interest are to be sequenced, an ordinary artisan would have been motivated to have employed the method taught by Drmanac, rather than experimenting to identify an appropriate sequencing method, in order to have saved time and reagents, for the advantages of convenience and cost effectiveness. Further, as Drmanac specifically teaches that the use of universal primers complementary to adaptors provides for efficient amplification of multiple target molecules using a single primer pair, an ordinary artisan would have been motivated to have modified the method of Gu et al so as to have performed adaptor ligation and amplification with universal primers for the advantage of efficiency.

11. Claims 37, 39, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al in view of Drmanac, as applied to claims 33-35, above, and further in view of Landegren et al.

The combined teachings of Gu et al and Drmanac do not teach or suggest employing in their methods steps of single-base extension, hybridization to an array, and/or oligo ligation, as required by claims 37, 39, and 41. Landegren et al teach that each of these procedures are well known methods for rapid detection and differentiation of SNP's (see entire reference). Specifically, Landegren et al disclose that minisequencing of SNPs, which comprises a step of single base extension, may be used for rapid analysis of multiple SNPs in a homogeneous format (p. 773). Similarly, Landegren et al teach that array hybridization may allow one to "analyze many SNPs in parallel" (p. 771) and, in combination with multiplex amplification, "greatly extend the number of SNPs analyzed at one time" (p. 774). Landegren also teaches that SNP analysis by oligonucleotide ligation assay permits rapid, real-time detection of SNPs in a homogeneous format (p. 772-773). In view of the teachings of Landegren et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the "analyzing" step (step (c)) of the method of Gu et al in view of Drmanac method so as to have conducted "analysis" to "assess the genotype at one or more polymorphic sites" using steps of single-base extension, hybridization to an array, and/or oligo ligation. An ordinary artisan would have been motivated to have made such a modification in order to have rapidly identified multiple

polymorphisms in a homogeneous format, as taught by Landegren et al, for the advantages of improved efficiency and ease of detection.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The New England Biolabs catalog (New England Biolabs, Inc., 1992, p. 136-137, 191-192) teaches that the frequency with which a restriction enzyme cleaves DNA varies from sample to sample (p. 191-192). The catalog further demonstrates that it is an inherent property of at least some of the enzymes taught by Gu et al that these enzymes cut DNA from at least some sources "on average about once every 2000 base pairs" (e.g., *Ava*I cleaves pUC19 once, *Bst*N1 cleaves ϕX174 twice) (p. 136-137).

13. It is noted that the formal drawings have been approved by the Draftsperson.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

September 8, 2000

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

9/10/00